Reactions of alpha,beta-unsaturated Thioamides with Diazo compounds

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Abstract: Several reactions of the a,b-unsaturated thioamide 8 with diazo compounds 1a–1d were investigated. The reactions with CH2N2 (1a), diazocyclohexane (1b), and phenyldiazomethane (1c) proceeded via a 1,3-dipolar cycloaddition of the diazo dipole at the C=C bond to give the corresponding 4,5-dihydro-1H-pyrazole-3-carbothioamides 12a–12c, i.e., the regioisomer which arose from the bond formation between the N-terminus of the diazo compound and the C(alpha)-atom of 8. In the reaction of 1a with 8, the initially formed cycloadduct, the 4,5-dihydro-3H-pyrazole-3-carbothioamide 11a, was obtained after a short reaction time. In the case of 1c, two tautomers 12c and 12c' were formed, which, by derivatization with 2-chlorobenzoyl chloride 14, led to the crystalline products 15 and 15'. Their structures were established by X-ray crystallography. From the reaction of 8 and ethyl diazoacetate (1d), the opposite regioisomer 13 was formed. The monosubstituted thioamide 16 reacted with 1a to give the unstable 4,5-dihydro-1H-pyrazole-3-carbothioamide 17.

DOI: https://doi.org/10.1002/hlca.200690252

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Reactions of α,β-Unsaturated Thioamides with Diazo Compounds

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[1]) Part of the projected Ph.D. thesis of *D. H. E.*, University of Zürich, 2006.

Several reactions of the α,β-unsaturated thioamide **8** with diazo compounds **1a-1d** were investigated. The reactions with CH_2N_2 (**1a**), diazocyclohexane (**1b**), and phenyldiazomethane (**1c**) proceeded *via* a 1,3-dipolar cycloaddition of the diazo dipole at the C,C-double bond to give the corresponding 4,5-dihydro-1*H*-pyrazole-3-thiocarboxamide **12a**-**12c**, *i.e.*, the regioisomer which arose from the bond formation of the N-terminus of the diazo compound with the α-C-atom of **8**. In the reaction of **1a** with **8**, the initially formed cycloadduct, the 4,5-dihydro-3*H*-pyrazole **11a**, was obtained after short reaction time. In the case of **1c** two tautomers **12c** and **12c'** were formed, which, by derivatization with 2-chlorobenzoyl chloride **14**, led to the crystalline products **15** and **15'**. Their structures were established by X-ray crystallography. In the reaction of **8** and ethyl diazoacetate (**1d**), the opposite regioisomer **13** was formed. The monosubstituted thioamide **16** reacted with **1a** to give the unstable 4,5-dihydro-1*H*-pyrazole-3-thiocarboxamide **17**.

1. Introduction. – In the last twenty years, reactions of thioketones with diazo compounds have been investigated extensively. It is generally accepted that the attack of the diazo compound **1** at the thioketone **2** leads to a 2,5-dihydro-1,3,4-thiadiazole **3**, which, in general, at room temperature is not stable and undergoes a 1,3-dipolar cycloreversion by elimination of N_2 to give the intermediate thiocarbonyl ylide **4**. This reactive intermediate can undergo different reactions to yield stable products (for reviews see [1][2]). On the one hand, a 1,3-dipolar electrocyclization can take place to give the thiirane **5**, or, by subsequent desulfurization, to yield the olefin **6**. On the other hand, **4** can react with a dipolarophile in a 1,3-dipolar cycloaddition to give the corresponding heterocycles **7** (*Scheme 1*). Furthermore, stabilization of **4** *via* dimerization or [1,4]H shift have also been reported.

Scheme 1

Investigations concerning 1,3-dipolar cycloadditions of diphenyldiazomethane (**1**, $R^1 = R^2 = Ph$) with different dipolarophiles by *Huisgen* and *Langhals* have shown that thiones **2**, especially aromatic ones, react extremely fast with diazo compounds and, therefore, were denominated as "superdipolarophiles" [3]. Thioamides have not been included in these comparative studies, but amino substituents in 4-position of thiobenzophenone led to a decrease of the reaction rate. As diazo compounds are classified as relatively electron-rich dipoles [4] and, therefore, electron-poor dipolarophiles are suitable for an optimal HOMO-LUMO-interaction [5], it is a moot point whether thioamides, as relatively electron-rich dipolarophiles undergo a 1,3-dipolar cycloaddition with diazo compounds and the subsequent cycloreversion to give the intermediate thiocarbonyl ylides. Studies of *El-Sharif et al.* have shown that, in some cases, it is possible to generate thiocarbonyl ylide intermediates from

thioamides, which led *via* 1,3-dipolar electrocyclization and subsequent desulfurization to the corresponding olefins [6].

The aim of the present work was to clarify whether unsaturated thioamides like (*E*)-*N*,*N*-diethylbut-2-enethioamide (**8**) react with diazo compounds in the manner described above, or if the dipolarophilicity of the C,C-double bond exceeds that of the C=S group. If the cycloaddition at the C=S group would be preferred, a thiocarbonyl ylide of type **9** with an extended π-system (*i.e.* R^2 = MeCH=CH) could be formed (*Scheme 2*). The latter should be able to undergo a 1,5-dipolar electrocyclization to give 2,3-dihydrothiophene **10**. Analogous 1,5-dipolar electrocyclizations of thiocarbonyl ylides bearing C=O [7-9] (and refs. cited therein), C=S [9], and C=N groups [10] have been reported recently.

Scheme 2

2. Results and Discussion. – Solutions of thioamide **8** [11] in CH_2Cl_2 reacted with different diazo compounds at room temperature without any catalyst within a few hours or days to give the corresponding 1:1 adducts in good yields. According to the MS- and NMR-spectra, the resulting products have not been formed by an attack of the diazo compound at the thiocarbonyl group as it was observed in the cases of the reactions with thioketones [7-9]. In the ^{13}C-NMR spectra of the products, a signal at *ca.* 190 ppm, which is characteristic for the thioamide C-atom was present, and the CI-MS spectra showed a $[M + 1]^+$-peak of the 1:1-adducts indicating that no N_2 elimination occurred. Thus, we proposed a 1,3-dipolar cycloaddition of the diazo component at the C,C-double bond conjugated with the C=S group. The formation of an intermediate thiocarbonyl ylide can be consequently excluded.

Investigations of the main product of the reaction of **8** with diazomethane (**1a**) obtained after a reaction time of 1 d by using two-dimensional NMR- (HMBC) and ^{15}N-NMR methods show that it consists of a 4,5-dihydro-1*H*-pyrazole and a *N*,*N*-diethylthioamide group. If the reaction was quenched after 1 h by adding AcOH and the work up was carried out quickly, two isomeric products **11a** and **12a** were obtained, whereof **11a** disappeared after a few h to give **12a** (*Scheme 3*). The less stable isomer **11a** is the result of a 1,3-dipolar cycloaddition, and a subsequent rearrangement *via* a [1,3]-H shift and leads to the more stable product **12a**.

It is surprising that no further reaction of the rearranged product with the diazo component could be observed. In a control experiment, **1a** was added to the pure product **12a**, but even stirring of the mixture at room temperature for 2 d did not result in a new product.

Scheme 3

The reactions of **8** with diazocyclohexane (**1b**) and phenyldiazomethane (**1c**), respectively, occurred in a similar way. Although an intermediate could be detected by TLC - most likely the initial [2 + 3]-cycloadduct of type **11** – only **12b** was isolated in the first case (*Scheme 4*). Two isomeric 1:1 adducts were obtained in the reaction with **1c**, but none was the initial adduct of type **11**. Both isomers showed an NH absorption in the ^{1}H-NMR spectrum (*s* at 5.72-5.18 ppm) and a C=N signal at 155.6 ppm in the ^{13}C-NMR spectrum. The isomers could not be separated but interconverted quickly. On this basis we proposed the two tautomeric structures **12c** and **12c'**. Derivatization with 2-chlorobenzoyl chloride led to the crystalline benzoyl derivatives **15** and **15'** (*Scheme 4*), which were separated by means of chromatography. Recrystallization from hexane/CH_2Cl_2 yielded suitable crystals for the X-ray crystal-structure determination (Figure).

Scheme 4

Figure

Since the space group of **15** is centrosymmetric, the compound in the crystal is racemic. The Me and Ph substituents on the five-membered ring are in a *cis* configuration. One of the Et groups of the diethylamino group is disordered over two equally occupied orientations as a result of random inversion of the position of the lone pair of electrons on the N-atom. The compound has crystallized in a space group that would allow for an enantiomerically pure compound, but refinement of the absolute structure parameter indicates that the crystals are most likely inversion twins. The five-membered ring of **15'** has a slightly flattened envelope conformation with atom C(5) as the envelope flap. The substituents at atoms C(4) and C(5) have a *trans* relationship.

The crystal-structure determination of the derivatives **15** and **15'** proved that the reaction of **8** with **1c** occurred regioselectively, but led to a mixture of two tautomers[2]), namely the 3-thiocarboxamide **12c** and the 5-thiocarboxamide **12c'** (*Scheme 4*). An explanation of the formation of **12c'** is the conjugation of the C=N bond with the Ph group at C(3).

The 1,3-dipolar cycloadditions of **8** with **1a**-**1c** proceeded all with the same regioselectivity, *i.e.*, the N-terminus of the diazo compound reacted with the α-C-atom of the thioamide to give the intermediate 4,5-dihydro-3*H*-pyrazole-3-

[2]) In the reaction of **8** with **1a** and **1b**, respectively, only the formation of the isomer with the C=N bond conjugated with the thioamide group, *i.e.* **12a** and **12b**, respectively, was observed.

thiocarboxamides of type **11** (*Scheme 3*)[3]). On the other hand, the addition of ethyl diazoacetate (**1d**), with **8** led to the 4,5-dihydro-1*H*-pyrazole **13** (*Scheme 4*), which bears the thiocarboxamide group at C(4). Therefore, the C-terminus of the diazo dipole reacted with the α-C-atom of the thioamide.

The reaction of the N-monosubstituted α,β-unsaturated thioamide **16** with **1a** at room temperature led within a few min to an unstable product, which decomposed quickly. The NMR-spectra of the crude product indicated the formation of the corresponding thioamide **17** with a 4,5-dihydro-1*H*-pyrazole residue (*Scheme 5*).

Scheme 5

3. Conclusions. – In all reactions of thioamide **8** with diazo compounds **1a-1d**, an addition of the dipole onto the C,C-double bond of **8** took place exclusively. Surprisingly, no addition onto the C=S group could be observed. The formed products are the corresponding dihydropyrazole thioamides **12a**-**12c** and **13**. In the cases of **12a-12c**, the products were formed in a regioselective cycloaddition, in which the N-terminus of the diazo compound added to the α-C-atom of **8**, followed by a [1,3]-H shift. The α,β-unsaturated thioamide **16** reacted with **1a** analogously, but the corresponding product **17** is extremely unstable. In the case of the reaction

[3]) This regioselectivity is supported by the examination of the orbital coefficients of the HOMO (**1a**, **1c**) and the LUMO (**8**) calculated with AMPAC version 8.16.7 with the AM1-Hamilton. Unfortunately, the results of the analogous calculations for the reaction with ethyl diazoacetate (**1d**) are not in accordance with the different regioselectivity of the cycloaddition. We thank *Dr. R. W. Kunz* for carrying out the calculations.

of **8** with **1d**, the C-terminus of the diazo compound added to the α-C-atom of **8** to give the opposite regioisomer **13**. In summary, in reactions with diazo compounds, the C=S group of α,β-unsaturated thioamides is less reactive than the C=C bond and therefore, thioamides of type **8** and **16** are no suitable precursors for the generation of thiocarbonyl ylides.

We thank the analytical units of our institute for spectra and analyses, and the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. *General.* See [9]. For the assignment of ^{15}N signals, ^{15}N-HMBC 2D-NMR methods were employed.

2. *Starting Materials.* The thioamides and diazo compounds were prepared following known protocols: diazomethane (**1a**) [13], diazocyclohexane (**1b**) [14], phenyldiazomethane (**1c**) [15], (*E*)-*N*,*N*-diethylbut-2-enethioamide (**8**) [11], *N*-methylprop-2-enethioamide (**16**) [16]. All other reagents are commercially available.

3. *Reaction of (*E*)-*N,N*-Diethylbut-2-enethioamide* (**8**) *with Diazo Compounds.*

3.1. N,N-*Diethyl-4,5-dihydro-4-methyl-3*H-*pyrazole-3-thiocarboxamide* (**11a**) *and* N,N-*Diethyl-4,5-dihydro-4-methyl-1*H-*pyrazole-3-thiocarboxamide* (**12a**). To a soln. of **8** (1.0 mmol) in CH_2Cl_2 (10 ml) was added drop-wise a soln. of **1a** (*ca.* 2 mmol) in Et_2O (6 ml). After 2 h, AcOH (*ca.* 10 drops) was added to quench the reaction. Purification of the crude product by CC (hexane/AcOEt 1:4 to 1:1) afforded 92 mg (45%) of **11a** and 66 mg (33%) of **12a**. Data of **11a**: R_f-value:

(hexane/AcOEt 1:1): 0.15. Yellowish oil. IR (neat): 3306*m*, 2971v*s*, 2934v*s*, 2873*s*, 1688*m*, 1549*m*, 1505v*s*, 1454v*s*, 1428v*s*, 1381v*s*, 1359v*s*, 1305v*s*, 1272v*s*, 1233v*s*, 1139*s*, 1095*s*, 1077*s*, 980*w*, 921*m*, 888*w*, 856*w*, 836*m*, 783*w*, 757*w*, 736*m*. ^{1}H-NMR: 5.26–5.23 (*m*, HC(3)); 4.95–4.85 (*dq*-like, 1 H of $H_2C(5)$); 4.39–4.14 (*m*, 1H of $H_2C(5)$, MeC*H*$_2$N); 3.96–3.76 (*m*, MeC*H*$_2$N); 3.00–2.91 (*m*, HC(4)); 1.44 (*t*, *J* = 7.2, *Me*CH_2N); 1.31 (*t*, *J* = 7.1, *Me*CH_2N); 1.03 (*d*, *J* = 7.1, *Me*CH(4)). ^{13}C-NMR: 194.3 (*s*, CS); 99.1 (*d*, C(3)); 85.4 (*t*, C(5)); 48.5, 46.5 (2*t*, 2 CH_2N); 33.2 (*d*, C(4)); 18.5 (*q*, *Me*C(4)); 14.1, 10.9 (2*q*, 2 *Me*CH_2N). CI-MS (NH_3): 200 (100, $[M + 1]^+$), 172 (33, $[M + 1 - N_2]^+$).

Data of **12a**: R_f-value: (hexane/AcOEt 1:1): 0.1. Yellowish oil. IR (neat): 3295*m*, 2971*m*, 2934*m*, 2872*w*, 1502v*s*, 1431*s*, 1379*m*, 1360*w*, 1344*w*, 1304*m*, 1271*s*, 1251*m*, 1227*w*, 1208*m*, 1140*m*, 1114*w* 1076*w*, 1003*w*, 969*w*, 921*w*, 819*w*, 779*w*, 760*w*. ^{1}H-NMR: 5.50–5.00 (br. *s*, NH); 4.41–4.27 (*m*, MeC*H*$_2$N); 4.15–3.97 (*m*, MeC*H*$_2$N, HC(4), 1 H of $H_2C(5)$), 3.39 (*t*, *J* = 8.1, 1 H of $H_2C(5)$); 1.65–1.53 (*m*, 2 *Me*CH_2N); 1.50 (*d*, *J* = 6.8, *Me*HC(4)). ^{13}C-NMR: 189.6 (*s*, CS); 156.7 (*s*, C(3)); 55.1 (*t*, C(5)); 47.8, 46.4 (2*t*, 2 CH_2N); 43.1 (*d*, C(4)); 15.5, 14.2 (2*q*, 2 *Me*CH_2N); 11.0 (*q*, *Me*HC(4)). CI-MS (NH_3): 200 (100, $[M + 1]^+$).

In an analogous experiment, to a soln. of **8** (1.3 mmol) in dry THF (10 ml) was added drop-wise a soln. of **1a** (*ca.* 3 mmol) in THF (*ca*. 8 ml). Then, the mixture was stirred for 1 day at r.t. Purification of the crude product by CC (hexane/AcOEt 1:2) afforded 218 mg (84%) of (**12a**) as a single product.

3.2. N,N-*Diethyl-4-methyl-1,2-diazaspiro[4.5]deca-2-en-3-thiocarboxamide* (**12b**). To a soln. of **8** (200 mg, 1.3 mmol) in CH_2Cl_2 (10 ml) was added drop-wise a soln. of **1b** (*ca.* 2 mmol) in CH_2Cl_2 (40 ml) and the mixture was stirred at r.t. for 6 h. Purification of the crude product by CC (hexane/AcOEt 1:2) afforded 283 mg

(81%) of **12b**. Yellowish crystals. M.p. 74–76°. IR (KBr): 3329*s*, 2966*m*, 2928*vs*, 2856*m*, 1622*w*, 1579*m*, 1512*vs*, 1451*s*, 1437*s*, 1405*m*, 1372*m*, 1356*m*, 1319*w*, 1297*m*, 1285*m*, 1267*s*, 1248*s*, 1209*m*, 1135*m*, 1097*m*, 1075*m*, 1061*m*, 1039*w*, 1019*m*, 981*w*, 948*m*, 936*w*, 916*m*, 855*w*, 844*w*, 831*w*, 809*w*, 781*m*, 738*s*, 698*s*, 666*vs*. ^{1}H-NMR: 5.2–4.7 (br. *s*, NH); 4.00–3.90, 3.73–3.65 (2*m*, 2 CH_2N); 3.31 (*q*, *J* = 7.3, HC(4)); 1.58–1.37 (*m*, 5 CH_2); 1.36–1.13 (*m*, 2 *Me*CH_2N); 0.96 (*d*, *J* = 7.3, MeC(4)). ^{13}C-NMR: 190.0 (*s*, CS); 156.4 (*s*, C(3)); 67.0 (*s*, C(5)); 50.3 (*d*, C(4)); 47.8, 46.5 (2*t*, 2 CH_2N); 36.3, 30.3, 25.4, 23.5, 22.6 (5*t*, cyclohexyl CH_2); 14.3, 11.0 (2*q*, 2 *Me*CH_2N); 10.1 (*q*, *Me*C(4)). EI-MS: 267 (86, $M^{+\cdot}$), 252 (41, [*M* – Me]$^+$), 224 (56, [*M* – Me – N_2]$^+$), 151 (36, [*M* – $SNEt_2$]$^+$), 98 (59, $C_6H_{12}N^+$), 72 (100, Et_2N^+).

3.3. N,N-*Diethyl-4,5-dihydro-4-methyl-5-phenyl-1*H-*pyrazole-3-thiocarboxamide* (**12c**) *and* N,N-*Diethyl-4,5-dihydro-4-methyl-3-phenyl-1*H-*pyrazole-5-thiocarboxamide* (**12c'**)[4]). To a soln. of **8** (843 mg, 5.2 mmol) in toluene (30 ml) was added drop-wise a soln. of **1c** (*ca.* 7 mmol) in toluene (150 ml) over a period of 3 d. Purification of the crude product by CC (hexane/AcOEt 8:1 to 2:1) afforded 563 mg (52%) of a mixture of the two isomeric thioamides **12c** and **12c'** as an oil and 197 mg of the starting material. Data of **12c**: ^{1}H-NMR: 7.74–7.69 (*d*-like, 1 arom. H); 7.43–7.31 (*m*, 4 arom. H); 5.72–5.18 (*br. s*, NH); 4.41 (*d*, *J* = 2.8, HC(5)); 4.25–3.62 (*m*, 2 CH_2N); 3.54 (*dq*; *J* = 2.8, 7.2, HC(4)); 1.52 (*d*, *J* = 7.2,

[4]) The tautomers **12c** and **12c'** could not be separated by HPLC because of a fast tautomerization. As it was not possible to isolate one of the two isomers in pure form, the correlation of the NMR signals with the arom. C-atoms and Et groups are not absolutely clear.

MeC(4)); 1.44-1.32 (*m*, 2 *Me*CH_2N). ^{13}C-NMR: 201.5 (*s*, CS); 155.6 (*s*, C(5)); 131.5 (*s*, 1 arom. C); 128.4, 127.5, 126.4 (3*d*, 5 arom. CH); 71.6 (*d*, C(3)); 48.7 (*t*, CH_2N); 48.0 (*d*, C(4)); 45.5 (*t*, CH_2N); 17.9 (q, *Me*C(4)); 14.3, 13.3 (2*q*, 2 *Me*CH_2N). CI-MS (NH_3, mixture): 276 (100, $[M + 1]^+$), 264 (36).

Data of **12c'**: ^{1}H-NMR: 7.74-7.69 (*d*-like, 1 arom. H); 7.43–7.31 (*m*, 4 arom. H); 5.72–5.18 (*br. s*, NH); 5.11 (*d*, *J* = 10.1, HC(3)); 4.25–3.79 (*m*, 2 CH_2N, HC(4)); 1.44–1.32 (*m*, 2 *Me*CH_2N); 0.77 (*d*, *J* = 8.4, MeC(4)). ^{13}C-NMR: 189.2 (*s*, CS); 155.6 (*s*, C(3)); 137.7 (*s*, 1 arom. C); 128.8, 128.3, 127.2 (3*d*, 5 arom. CH); 68.3 (*d*, C(5)); 47.9 (*t*, CH_2N); 46.8 (*d*, C(4)); 46.7 (*t*, CH_2N); 11.3 (*q*, *Me*C(4)); 11.0, 10.9 (2*q*, 2 *Me*CH_2N).

3.4. N,N-*Diethyl-1-(2-chlorobenzoyl)-4,5-dihydro-4-methyl-5-phenyl-1*H-*pyrazole-3-thiocarboxamide* (**15**) *and* N,N-*Diethyl-1-(2-chlorobenzoyl)-4,5-dihydro-4-methyl-3-phenyl-1*H-*pyrazole-5-thiocarboxamide* (**15'**). To a soln. of a mixture of **12c** and **12c'** (275 mg, 1 mmol) in CH_2Cl_2 (20 ml) was added 2-chlorobenzoyl chloride (**14**, 174 mg, 1 mmol) and Et_3N (111 mg). After 15 min, the mixture was poured on ice (50 g) and diluted with CH_2Cl_2 (30 ml). After separation of the two phases, the aq. phase was extracted with CH_2Cl_2, the org. phase was dried ($MgSO_4$), and the solvent was evaporated. Purification of the crude product by CC (hexane/AcOEt 5:1) afforded 163 mg of **15** (40%), 100 mg of **15'** (25%), and 84 mg (20%) of a mixture of the two isomers. Data of **15**: Yellowish crystals. M.p. 161–162°. IR (Golden Gate ATR): 3056*w*, 3031*w*, 2973*w*, 2935*w*, 2874*w*, 1634*m*, 1594*w*, 1579*w*, 1508*m*, 1493*w*, 1473*m*, 1444*m*, 1422*m*, 1380*w*, 1363*w*, 1309*w*, 1297*w*, 1282*w*, 1264*m*, 1253*m*, 1221*m*, 1201*w*, 1173*w*, 1139*m*, 1092*w*, 1076*w*, 1055*m*, 1037*w*, 979*w*, 918*w*, 841*m*, 822*m*, 772*m*, 746*s*, 691*s*. ^{1}H-NMR: 7.40–7.25 (*m*, 9 arom. H); 5.74 (*d*, *J* = 11.6, HC(5)); 4.41 (*dq*, *J* = 11.6, 7.6, HC(4)); 4.21–4.10 (*m*, 1 H of CH_2N); 3.83–3.64 (*m*, 2 H of 2 CH_2N); 3.58–3.47 (*m*, 1 H of CH_2N);

1.24, 1.11 (2*t*, *J* = 7.1, 2 *Me*CH_2N); 0.76 (*d*, *J* = 7.6, MeC(4)). ^{13}C-NMR: 187.1 (*s*, CS); 165.7 (*s*, CO); 158.4 (*s*, C(3)); 135.8, 130.8 (2*s*, 2 arom. C)[5]); 130.2, 129.1, 128.8, 128.5, 127.8, 126.8, 126.5 (7*d*, 9 arom. CH); 64.0 (*d*, C(5)); 48.3 (*t*, CH_2N); 47.7 (*d*, C(4)); 46.4 (*t*, CH_2N); 14.1 (*q*, *Me*C(4)); 11.9, 10.8 (2*q*, 2 *Me*CH_2N). CI-MS (NH_3): 416 (41), 415 (25), 414 (100, $M^{+\cdot}$). Anal. calc. for $C_{22}H_{24}ClON_3S$ (413.96): C 63.83, H 5.84, Cl 8.56, N 10.15, S 7.75; found: C 63.80, H 5.77, Cl 8.56, N 10.07, S 7.84.

Crystals suitable for the X-ray crystal-structure determination were grown from CH_2Cl_2/hexane by slow evaporation of the solvent.

Data of **15'**: Colorless crystals. M.p. 176–179°. IR (Golden Gate ATR): 3066*w*, 2975*w*, 2939*w*, 2873*w*, 2833*w*, 1982*w*, 1962*w*, 1839*w*, 1637*m*, 1592*w*, 1567*w*, 1503*m*, 1454*m*, 1440*m*, 1421*m*, 1378*w*, 1306*w*, 1224*w*, 1155*w*, 1089*w*, 1059*w*, 833*w*, 784*m*, 770*m*, 745*m*, 692*m*. ^{1}H-NMR: 7.62–7.57 (*m*, 3 arom. H); 7.43–7.26 (*m*, 6 arom. H); 5.35 (*d*, *J* = 3.3, HC(3)); 4.26–4.07 (*m*, 2 H of 2 CH_2N); 4.26–3.67 (*m*, 2 H of CH_2N, HC(4)); 1.49–1.44 (*m*, *Me*CH_2N, MeC(4)); 1.32 (*t*, *J* = 7.1, *Me*CH_2N). ^{13}C-NMR: 198.4 (*s*, CS); 165.3 (*s*, CO); 159.4 (*s*, C(5)); 135.2, 131.3 (2*s*, 2 arom. C)[6]); 130.3, 130.0, 129.7, 129.1, 128.5, 127.2, 126.3 (7*d*, 9 arom. CH); 68.5 (*d*, C(3)); 49.0 (*t*, CH_2N); 48.9 (*d*, C(4)); 46.5 (*t*, CH_2N); 18.5, 14.5, 10.9 (3*q*, 2 *Me*CH_2N, *Me*C(4)). CI-MS (NH_3): 416 (45), 415 (27), 414 (100, $M^{+\cdot}$).

Crystals suitable for the X-ray crystal-structure determination were grown from CH_2Cl_2/hexane by slow evaporation of the solvent.

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[5]) The signal of the arom. CCl could not be detected. Perhaps the signal overlaps with the signal at 135.8 ppm, which is more intensive than expected.

[6]) The signal of the arom. CCl could not be detected.

3.5. *4-Ethyl (*N,N-*Diethylthiocarbamoyl)-4,5-dihydro-5-methyl-1*H-*pyrazole-3-carboxylate* (**13**). To a soln. of **8** (200 mg, 1.3 mmol) in CH_2Cl_2 (10 ml) was added drop-wise a soln. of **1d** (*ca.* 6 mmol) in CH_2Cl_2 (20 ml) over a period of 3 d whereas the mixture was maintained at 45°. Purification of the crude product by CC (hexane/AcOEt 1:2) afforded 184 mg (50%) of **13**. IR (KBr): 3315*m*, 2978*s*, 2935*s*, 2874*m*, 1703v*s*, 1578*s*, 1503v*s*, 1450v*s*, 1426v*s*, 1374*s*, 1344*s*, 1304*s*, 1272v*s*, 1223v*s*, 1172*m*, 1132v*s*, 1079v*s*, 1019v*s*, 942*w*, 921*w*, 831*m*, 770*m*, 739*m*. ^{1}H-NMR: 7.45–6.80 (br. *s*, NH); 4.32 (*d*, *J* = 3.3, HC(4)); 4.28 (*q*, *J* = 7.1, CH_2O); 4.19 (*m*; 1 H of CH_2N); 3.80–3.66 (*m*, 2 H of 2 CH_2N); 3.62–3.50 (*m*, 1 H of CH_2N); 3.25 (*dq*, *J* = 7.2, 3.3, HC(5)); (*d*, *J* = 7.2, MeC(5)); 1.38–1.32 (2*t*, *J* = 7.1, 7.2, *Me*CH_2O, *Me*CH_2N); 1.28–1.25 (*t*, *J* = 7.1, *Me*CH_2N). ^{13}C-NMR: 200.0 (*s*, CS); 161.8 (*s*, COOEt); 146.3 (*s*, C(3)); 72.3 (*d*, C(4)); 61.1 (*t*, CH_2O); 48.7 (*t*, CH_2N); 46.9 (*d*, C(5)); 45.3 (*t*, CH_2N); 17.4 (*q*, *Me*C(5)); 14.1 (*q*, *Me*CH_2O); 13.2, 10.8 (2*q*, 2 *Me*CH_2N). CI-MS (NH_3): 289 (9, $[M + NH_4]^+$), 272 (100, $[M + 1]^+$), 244 (34, $[M - N_2 + 1]^+$).

4. *Reaction of* N-*Methylprop-2-enethioamide* (**16**) *with* **1a**. To a soln. of **16** (2.0 mmol) in THF (10 ml) was added drop-wise a soln. of **1a** (*ca.* 3 mmol) in THF (8 ml) at r.t., and the mixture was stirred for 10 min. The crude product was purified by flash-CC (hexane/AcOEt 3:1 to 1:2): *ca.* 100 mg (*ca.* 50%) of *N*-methyl-4,5-dihydro-1*H*-pyrazole-3-thiocarboxamide (**17**). Yellowish oil[7]). ^{1}H-NMR: 8.60–8.10 (br. *s*, MeN*H*); 6.10–5.50 (br. *s*, HN(1)); 3.55–3.48 (*t*-like, $H_2C(5)$); 3.16 (*d*, MeN); 3.14–3.03 (*t*-like, $H_2C(4)$). ^{13}C-NMR: 188.3 (*s*, CS); 151.4 (*s*, C(3)); 49.3 (*t*, $H_2C(5)$); 32.5 (*t*, $H_2C(4)$); 31.9 (*q*, MeN).

[7]) The product **17** is extremely unstable.

5. *X-Ray Crystal-Structure Determination of* **15** and **15'** (*Table* and *Figure*)[8]). All measurements were performed on a *Nonius KappaCCD* diffractometer [17] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream* 700 cooler. The data collection and refinement parameters are given in the *Table*, and views of the molecules are shown in the *Figure*. Data reduction was performed with *HKL Denzo* and *Scalepack* [18]. The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [19] was applied. Equivalent reflections, other than *Friedel* pairs (in **15'**), were merged. The structures were solved by direct methods using SIR92 [20], which revealed the positions of all non-H-atoms. In the case of **15**, one of the Et groups of the Et_2N group is disordered over two orientations. Two sets of positions were defined for the atoms of this Et group and the site occupation factors of the major conformation refined to a value close to 0.5, so the site occupation factors were fixed at 0.5 thereafter. Similarity restraints were applied to the chemically equivalent bond lengths and angles involving the ordered and disordered Et groups, while neighboring atoms within and between each conformation of the disordered Et group were restrained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent atom ($1.5U_{eq}$ for the Me

[8]) CCDC- -contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Center via* http://www.ccdc.cam.ac.uk/data_request/cif.

groups). The refinement of the structures was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. In the case of **15**, 6 reflections, whose intensities were considered as extreme outliers, were omitted from the final refinement. Refinement of the absolute structure parameter [21] for **15'** yielded a value of 0.44(10), which indicates that the crystals are most likely inversion twins. Neutral atom scattering factors for non-H-atoms were taken from [22a], and the scattering factors for H-atoms were taken from [23]. Anomalous dispersion effects were included in F_c [24]; the values for f' and f'' were those of [22b]. The values of the mass attenuation coefficients are those of [22c]. All calculations were performed using SHELXL97 [25] program.

Table

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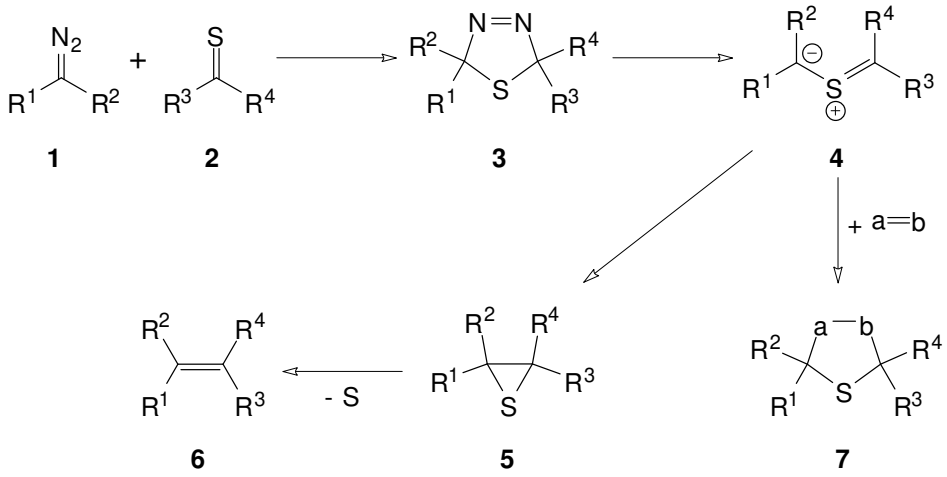
Legends

Figure. *ORTEP Plots* [12] *of the molecular structure of a) one of the two conformations of* **15***, and b)* **15'** (50% probability ellipsoids, arbitrary numbering of the atoms)

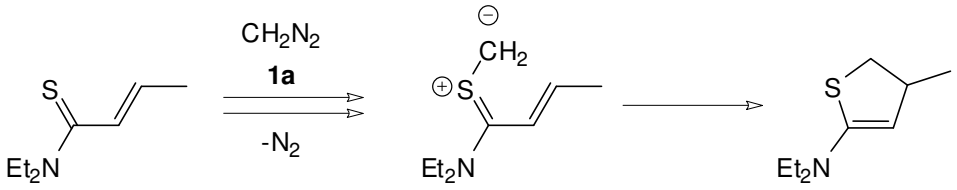
Table. *Crystallographic Data of Compounds* **15** *and* **15'**

	15	**15'**
Crystallized from	hexane/CH_2Cl_2	hexane/CH_2Cl_2
Empirical formula	$C_{22}H_{24}ClN_3OS$	$C_{22}H_{24}ClN_3OS$
Formula weight [g mol-1]	413.96	413.96
Crystal color, habit	yellow, prism	colorless, needle
Crystal dimensions [mm]	0.30 × 0.32 × 0.35	0.05 × 0.08 × 0.22
Temperature [K]	160(1)	160(1)
Crystal system	triclinic	orthorhombic
Space group	$P\bar{}$,1	$P2_12_12_1$
Z	2	4
Reflections for cell determination	16212	173390
2θ range for cell determination [°]	4 – 60	4 – 50
Unit cell parameters a [Å]	10.0771(2)	7.1060(2)
b [Å]	10.3993(2)	12.4905(4)
c [Å]	11.3362(2)	23.3874(8)
α [°]	77.840(1)	90
β [°]	65.069(1)	90
γ [°]	85.567(1)	90
V [Å^3]	1053.02(4)	2075.8(1)
D_x [g cm^{-3}]	1.305	1.324
μ(MoK_α) [mm^{-1}]	0.298	0.302
Scan type	ϕ and ω	ϕ and ω
2θ (max) [°]	60	50
Transmission factors (min; max)	0.761; 0.915	0.794; 1.002
Total reflections measured	27147	29663
Symmetry-independent reflections	6137	3662
Reflections with $I > 2\sigma(I)$	5049	3178
Reflections used in refinement	6131	3662
Parameters refined; restraints	276; 48	258
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0465	0.0518
$wR(F^2)$ (all data)	0.1270	0.1192
Weighting parameters (a; b)[a]):	0.0645; 0.353	0.0458; 1.7391
Goodness of fit	1.062	1.130
Secondary extinction coeff.	0.27(1)	0.025(2)
Final Δ_{max}/σ	0.001	0.001
$\Delta\rho$(max; min) [e Å^{-3}]	0.51; -0.45	0.25; -0.27

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$

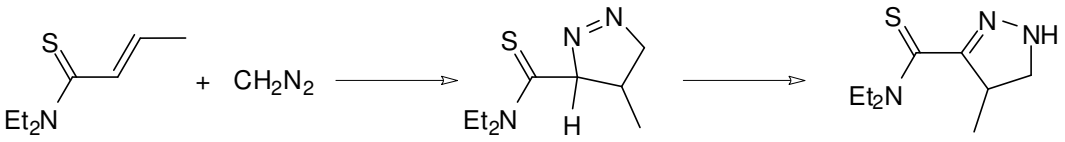


Scheme 1



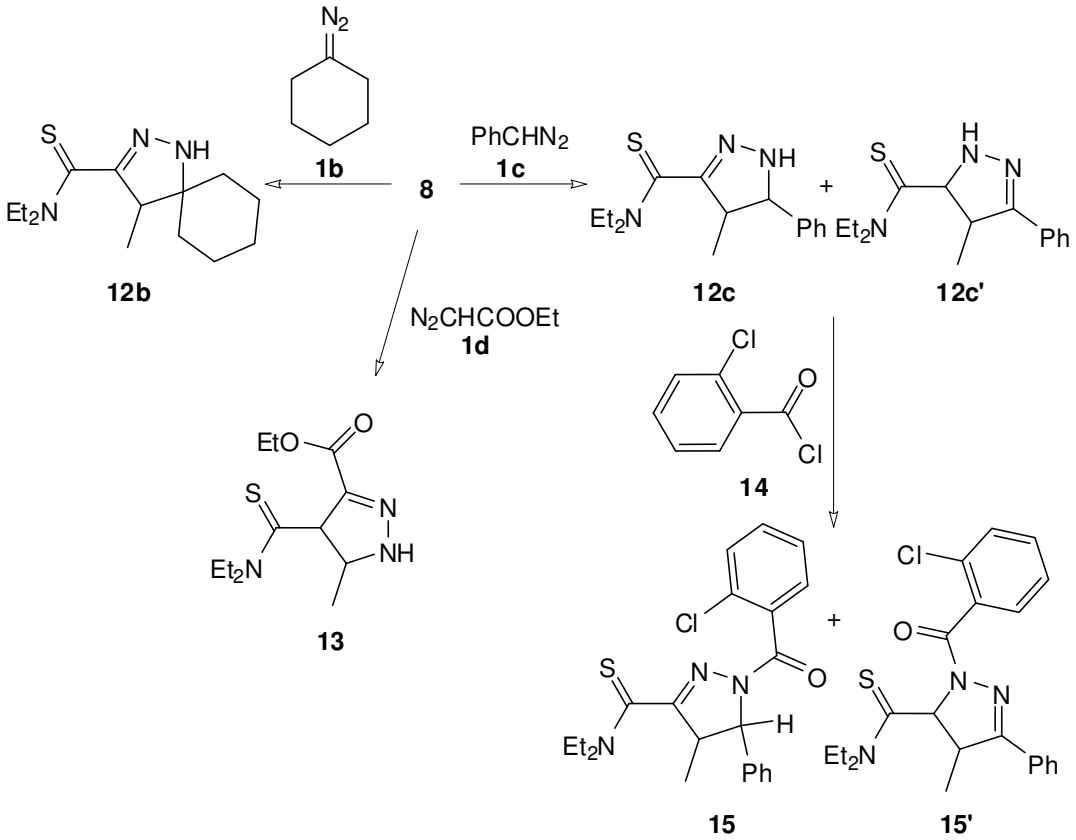
8 **9** **10**

Scheme 2

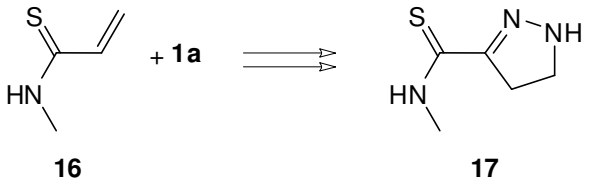


8 **1a** **11a** **12a**

Scheme 3

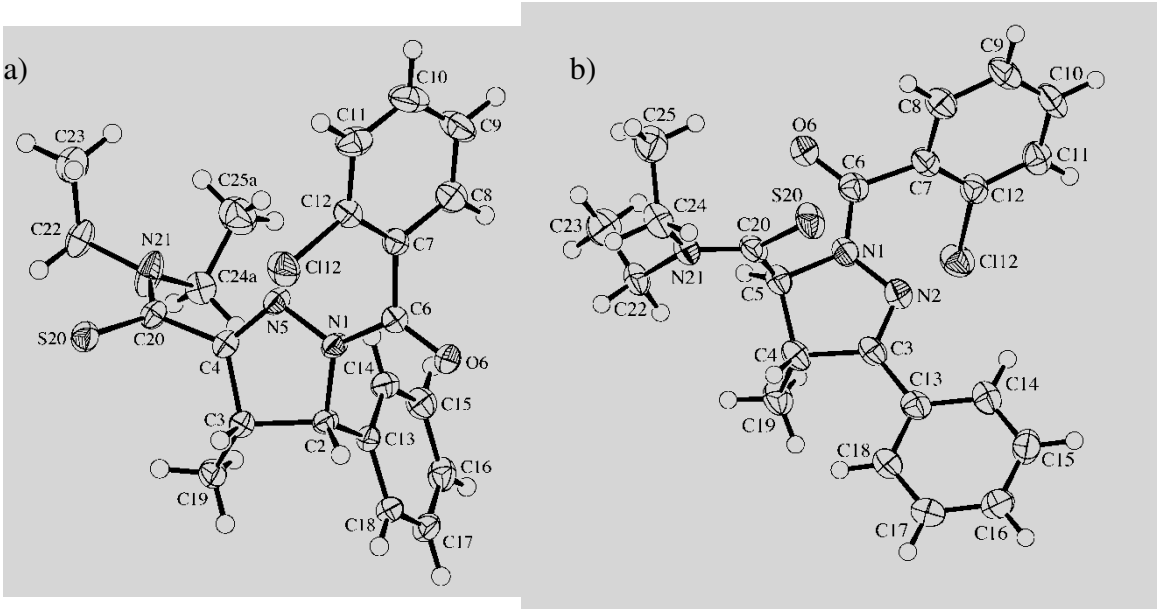


Scheme 4



16 **17**

Scheme 5


a)
C10
C11
C9
C23
C25a
C12
C8
C22
N21
C7
C24a
Cl12
S20
C20
N5
N1
C6
C4
C14
O6
C3
C15
C2
C13
C16
C19
C18
C17
b)
C9
C10
C8
C25
O6
C6
C11
C7
C12
C24
S20
C23
C20
N1
Cl12
N21
C5
N2
C22
C4
C3
C13
C14
C19
C18
C15
C17
C16

Figure

Graphical Abstract